

Portal vein thrombosis in a pandemic era

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Abstract: Portal vein thrombosis (PVT) is the blockage or narrowing of the portal vein by a thrombus being a relatively rare condition, linked to the presence of an underlying liver disease or prothrombotic disorders. We present the case of a 55-year-old woman, who was rushed to a territorial hospital for abdominal pain in her right flank, accompanied by nausea and vomiting for about a week. Following clinical, paraclinical investigations and exploratory laparoscopy, the suspicion of transverse colon tumor was raised, later refuted by exploratory laparotomy that detected an enteromesenteric infarction in the ileum, with localized peritonitis, for which a segmental enterectomy with termino-terminal anastomosis was performed, with a slow favorable evolution. Two months later, the patient went to the "Sf Spiridon" Hospital in Iasi for transit disorders associated with rectal hemorrhages. Following paraclinical investigations, a co-infection with *Clostridium Difficile* and Sars-Cov-2 was identified, for which adequate treatment was lead, but with the persistence of rectorages, which is why a computed tomography (CT) scan was performed. Imaging revealed thrombosis of the port system and the superior mesenteric vein, and it was initiated anticoagulant therapy. The paper will help raise awareness of the complexity of cases associated with portal vein thrombosis.

Keywords: Portal vein thrombosis, Sars-Cov-2, *Clostridium difficile*, anticoagulant therapy, coagulopathy, D-dimeri

Introduction.

Portal vein thrombosis (PVT) is the blockage or narrowing of the portal vein by a thrombus being relatively rare, and the etiology was linked to the presence of an under-lying liver disease or prothrombotic disorders. The mechanism of PVT development is complex and multifactorial and not always attributable to a single risk factor [1, 2]. However, no cause is identified in more than 25% of patients [3]. The prevalence of PVT in the general population is about 1%, although it varies greatly among patient populations based on basic pathophysiology and etiology [4].

The pathophysiology of portal vein thrombosis comprises one or more features of

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the Virchow triad, namely, reduced portal blood flow, a hypercoagulable condition, or vascular endothelial lesions.

While PVT has been associated with some important clinical complications, including worsening portal hypertension (at least in the short term), mesenteric infarction and portal biliopathy, its overall prognostic significance is still not fully understood. PVT is clinically relevant where liver transplantation is anticipated [5].

PVT occurs either in association with cirrhosis or with a malignancy of the liver or may occur without an associated liver disease. PVT is a major cause of non-cirrhotic prehepatic portal hypertension worldwide. Balfour and Stewart described the first PVT case in 1868 in a patient with ascites, splenomegaly, and variceal dilatation [6]. PVT is found in up to 35% of cirrhotic patients with hepatocellular carcinoma [7,8]. Several causes may be involved in the pathogenesis of PVT and often several coexist. Inflammatory abdominal foci (such as appendicitis, diverticulitis, inflammatory bowel disease, pancreatitis, cholecystitis, liver abscesses and cholangitis), liver cirrhosis or tumors, are the most common local thrombotic risk factors [4, 9, 10].

Malignant tumors, often of hepatic or pancreatic origin, are responsible for 21% - 24% of all PVT cases [11].

Direct vascular invasion, tumor mass compression or a hypercoagulable condition are the mechanisms involved in the neoplastic development of PVT; hormonal factors may also play a role in this process, especially in men [12, 13, 14].

On the other hand, myeloproliferative disorders and prothrombotic disorders belong to the group of systemic risk factors, with a prevalence of approximately 40% and 60%, respectively. Leiden factor V mutation is the most common thrombophilia predisposing to PVT, followed by protein C deficiency [15,

16]. The role of protein S and antithrombin III deficiency in the etiology of PVT has not yet been confirmed. Antiphospholipid antibody syndrome, pregnancy and hormone therapies have also been associated with PVT [17].

Occasionally, it is not possible to recognize any overt cause of PVT; generally, the clinical course is favorable for these patients, with a low incidence of complications. However, at present, "idiopathic PVT" is less frequent, thanks to the amelioration in diagnosis and to a more scrupulous attention to patients' clinical history [18].

The onset of PVT can be acute or chronic. This is an arbitrary distinction, which is sometimes difficult to apply in clinical practice. Patients with symptoms such as abdominal pain, nausea, and fever about two months prior to hospitalization may develop acute PVT [19].

PVT means the development of thrombi in the extrahepatic portal venous drainage system of the liver. Jamieson [20], cited by Webster [21], classifies TP anatomically into four types: (1) limited to the portal vein beyond the confluence of the splenic vein; (2) extended to the superior mesenteric vein, but with patent mesenteric vessels; (3) extended to the entire splanchnic venous system, but with large collaterals; or (4) only with fine collaterals [20]. This classification is useful to evaluate the operability and clinical outcome of a patient. In fact, when thrombosis is extended to both portal and mesenteric veins, the risk of intestinal ischemia is considerable and mortality is high, despite a lower risk of variceal bleeding [22].

Clinically, intestinal congestion and ischemia are typical manifestations of acute PVT; Abdominal pain or distension, diarrhea, rectal bleeding, nausea, vomiting, anorexia,

fever, lactacidosis, splenomegaly and sepsis may be present variably [23, 24].

If the obstruction is not resolved quickly, intestinal perforation, peritonitis, shock and death may occur due to multiorgan failure [9]. Most patients have splenomegaly, while ascites is rare or eventually present before the development of collateral circulation. This mild, transient ascites is due to intestinal venous congestion in the absence of activated mechanisms in liver cirrhosis [23, 24].

For diagnosis, the most widely used are non-invasive imaging methods: color Doppler ultrasound, computed tomography with contrast or angio-MRI. Computed tomography is more useful than ultrasound in demonstrating portal cavernoma and venous collaterals. Ultrasonography is usually the most commonly used investigation with a sensitivity and specificity between 60% and 100% [25]. It can reveal the presence of solid material, hyperechoic, the presence of collateral vessels or a cavernoma [26, 27, 28].

Endoscopic ultrasonography demonstrated 93% specificity and 81% sensitivity in the diagnosis of PVT, being able to detect small and neo clonal thrombi. However, echo-endoscopy is limited due to the presence of a relatively blind area, which cannot be investigated, involving the distal superior mesenteric vein and the intrahepatic portion of the portal vein [29].

In patients with PVT, the liver function is usually preserved. Laboratory investigations will be normal or fairly normal, unless liver disease is associated. However, prothrombin levels and other coagulation factors could be moderately decreased, while D dimers are usually elevated [9, 29].

The prognosis varies depending on the etiological factors, but also on the time of diagnosis. Old age, malignancy, cirrhosis, mesenteric vein thrombosis, are associated

with reduced survival [30]. Systemic risk factors, such as myeloproliferative syndromes or other prothrombotic disorders, do not appear to affect short-term survival [31].

In addition, when recognized and treated before the onset of intestinal infarction, acute PVT has a good prognosis [32, 33]. In contrast, in cases of intestinal ischemia and dysfunction or multiple organ failure, the hospital mortality rate is about 20% -50% [34].

The overall initial goal of acute PVT treatment is to prevent the development of PVT-related complications, namely gastrointestinal bleeding, ascites, ischemic hepatitis, ischemia/intestinal infarction. Regarding chronic PVT, the goal of treatment is to repermeabilize the portal vein, in addition to preventing complications.

Today's clinical trials are, unfortunately, still insufficient in deciding the appropriate therapy for both acute and chronic PVT. Generally, if the risk of bleeding is low, it is reasonable to start treatment with oral anticoagulant therapy. Anticoagulation does not lyse the clots, but has some value for long-term prevention in hypercoagulable conditions, despite the risk of variceal bleeding.

Otherwise, management turns to portal hypertension and its complications; treatment may include octreotide IV (a synthetic analogue of somatostatin) and endoscopic banding to control variceal bleeding and non-selective beta-blockers to prevent bleeding. Invasive approaches - such as thrombolysis or trans-jugular portosystemic shunt are other treatment modalities [35].

The purpose of this review is the clinical presentation, diagnosis and management of acute and chronic PVT. The presence of PVT should be considered an indication for prothrombotic disorders, liver

disease and other local and general factors that need to be carefully investigated. It is hoped that this case report will help raise awareness of the complexity associated with portal vein thrombosis among the medical community.

Materials and Methods.

We present the case of a 55-year-old patient hospitalized in a local hospital 6 months ago for diffuse abominable pain with increased intensity in the right flank, nausea, vomiting, loss of appetite and abdominal bloating. From the pathological history, the patient is known to have hypertension and grade I obesity.

At the clinical examination - abdomen increased in volume due to adipose tissue, dullness exceeded on the flanks, spontaneous pain and palpation in the right flank; physiological intestinal transit.

Paraclinical investigations highlight inflammatory syndrome - leukocytosis with neutrophilia (WBC 25.84 x 103/μl, neutrophils 92.2%); thrombocytosis - 723 x103/μl, PCR 164mg/l; otherwise, hematological and biochemical parameters within normal limits. Abdominal ultrasound - difficult examination due to intense aerocolia, liver examined on intercostal sections, apparently homogeneous, normal size, undiluted portal vein, gallbladder without stones, with thin walls; unvisited pancreas; globular spleen; bilateral normal kidneys; free intraperitoneal fluid in medium. The puncture of the peritoneal fluid was performed - which highlights an infamous smear, with numerous intact or lysed PMNs and mesothelium, lymphocytes and red blood cells. Empty abdominal radiography showed a hydro-aerial image in the middle 1/3 of the abdomen. Chest radiography - hilarious images of increased intensity and area, moderate accentuated bilateral hilio-basal lung pattern.

The upper digestive endoscopy performed objectified the absence of esophageal varices, gastric body compressed on the great gastric curvature, slightly congestive antral mucosa, extrinsically deformed gastric angle, permeable pylorus, duodenum - mucosa with normal appearance.

The patient was also evaluated by lower digestive endoscopy - anal fissure, otherwise mucous of normal appearance up to the splenic angle, then the investigation cannot be continued.

In the absence of elements of liver disease to justify the presence of free intraperitoneal fluid (normal transaminases, normal prothrombin time; absence of endoscopic and ultrasound signs of portal hypertension), following clinical examination in conjunction with paraclinical examinations and exploratory laparoscopy - the suspicion was raised for transverse colon tumor, later refuted by exploratory laparotomy that detected an entero-mesenteric infarction in the ileum, with localized peritonitis. Segmental enterectomy with termino-terminal anastomosis and peritoneal drainage was performed.

During hospitalization, the evolution was slowly favorable, associating an infection with *Clostridium Difficile*, for which antibiotic therapy was instituted, with negation of toxins A and B, remission of the important inflammatory syndrome and, subsequently, the patient's discharge. One week after discharge, the patient returns to the emergency room with an affected general condition, significant abdominal pain, being hospitalized for the evaluation and treatment of a blocked evisceration complicated by a suppuration in the wound, associating the infection with Sars-Cov-2.

At the biological examination presents thrombocytosis - 540 x 103/μl; hepatic cyto-lysis syndrome, anicteric cholestasis syndrome, hypoalbuminemia,

PCR 51.5mg/l. Bio-logical samples collected from the wound showed infection with *Pseudomonas aeruginosa* - for which antibiotic therapy was instituted according to the antibiogram, followed by serial excisional debridement's, with favorable evolution of the wound and secondary suture.

In January 2021, the patient came to the Emergency Hospital "St. Spiridon" from Iasi for the evaluation of an accelerated intestinal transit associated with rectoris. Following paraclinical investigations, we observe absence of anemia, moderate thrombocytosis ($455 \times 10^3/\mu\text{l}$), absence of inflammation, mild hypoproteinemia, normal transaminases, positive occult hemorrhage test.

At colonoscopic reassessment - at the level of the sigmoid congestive mucosa. Up to 30 cm from the anal mucosal margin was without lesions, subsequently the investigation cannot be continued due to severe pains accused by the patient. Due to the persistence of accelerated intestinal transit, the consumption of antibiotics recently for wound infection, the suspicion of relapse of *Clostridium Difficile* infection is raised.

Following the sampling, toxins A and B were positive, antibiotic treatment was instituted with metronidazole and vancomycin, with the normalization of stool frequency, but with the persistence of rectorages but also abdominal pain.

Considering the symptomatology, the patient was evaluated by abdomino-pelvic CT, which aims at: large liver at the base of the left lobe - 65 mm, with diffuse perfusion disorders, without portal nodular lesions; cavernom portal; perigastric, mesenteric collateral circulation and at the level of the abdominal wall; the absence of contrast at the level of the segmental branches, the right, left branch, the trunk of the portal vein, which extends to the level of the spleno-mesenteric

confluence and to the level of the superior mesenteric vein, along its entire length (Figure 1a.b.c); permeable splenic vein, with in-homogeneous contrast (partially thrombosed); permeable upper and lower mesenteric arteries; spleen of increased size ~ 112/50/120 mm (maximum axial diameter/thickness/cranio-caudal length); splenic index of 672 (normal ≤ 480); splenic volume 420 ml (normal 110-340 ml); homogeneous structure; median-line eventration in meso- and hypogastrium, measuring 25/67/140 mm, with epiploic content and conglomerate, undiluted, small intestine loops mesenteric level; numerous mesenteric lymphadenopathy with short infracentimetric axis; check and ascending colon with thickened wall ~ 5 mm; liquid blade in the root of the mesentery of approx. 5 mm; 8 mm pelvic fluid blade; 9 mm pericardial fluid blade.



Figure 1a. ; Figure 1b.



Figure 1c (sagittal view).

Figure 1(a, b, c). Absence of contrast at the level of the segmental branches, the right, left branch, the trunk of the portal vein, which extends to the level of the spleno-mesenteric con-fluence and to the level of the superior mesenteric vein, along its entire length.

Given the ongoing evolution, CT examination provided important information on the diagnosis and therapeutic conduct. The patient benefited from a hematological consultation, which recommended completing the biological picture with the thrombophilic profile, which reveals MTHFR (methylenetetrahydrofolate reductase) A1298C heterozygous mutant and PAI-1 4G/4G homozygous gene. The profile of antiphospholipid antibodies, protein C, protein S, antithrombin III - being within normal parameters.

Results.

Once the diagnosis of PVT was established on the background of a thrombophilia, the anticoagulant treatment with low molecular weight heparin was initiated in order to prevent the development of complications related to PVT, but also to repermeabilization of the portal vein.

The peculiarity of the case is represented by the porto-mesenteric thrombosis with uncharacteristic symptoms for diagnosis, in a patient with a background

of thromophilia, and co-infection with *Clostridium difficile* and Sars-Cov2. Abdominal ultrasound and examination in Doppler mode, in difficult conditions - less sensitive in visualization of related portal venous areas, including mesenteric, led to delayed diagnosis of PVT.

Discussion.

From the first description of portal venous thrombosis (PVT) by Balfour and Stewart in 1869, in their report on a 20-year-old patient who died of complications of splenomegaly, ascites and varicose dilatation with associated PVT, clinical manifestations and management of PVT were greeted with great interest [6].

The natural history of PVT has not been well described due to the wide variability of the underlying causes and patient-specific determinants, such as associated prothrombotic status and vascular or hepatic physiology.

It is important to remember that in the initial diagnosis of PVT, 10-15% of patients do not have known risk factors. In these non-cirrhotic patients, the assessment of the presence of myeloproliferative disorder, thrombophilia or occult malignancy should be considered. Recently, the presence of the JAK2 V617 mutation has been shown to be extremely suggestive for myeloproliferative neoplasms and was found in 5-35% of patients with PVT [36, 37].

In these patients, a hematological investigation including bone marrow biopsy should be performed to establish the diagnosis of myeloproliferative neoplasia and to guide further treatment. In addition, deletion and/or insertion mutations of exon 9 in the calreticulin gene (CALR) have recently been associated with myeloproliferative neoplasms [38].

However, CALR gene mutations are apparently associated with a lower risk for PVT than the JAK2 V617 mutation [39].

Levels of protein S, protein C, antithrombin antigen, and antiphospholipid antibodies are often initially dosed to detect suspected thrombophilia. However, these tests have been shown to be inadequate and should be replaced by appropriate functional tests to define thrombophilia phenotypes or by selected genetic tests, such as for factor V Leiden [40].

Some studies on thrombophilia by D Amico et al. showed that myeloproliferative disorders were the most common cause in patients with PVT, and in patients with thrombophilia and PVT PAI-1 4G-4G (inhibitor of plasminogen activator type 1-4G/4G genotype) was the most common cause (55, 5%), followed by MTHFR mutation (28.6%), Leiden factor V mutation (7.4%) and prothrombin gene mutation (7.4%) [41]. Meta-analysis on thrombophilia in portal venous thrombosis showed the prevalence of antithrombin III deficiency in 3.9%, protein C deficiency in 5.6% and protein S deficiency in 2.6% of patients. [42] Heterozygous MTHFR was reported in 21% of patients with PVT, while homozygous MTHFR was not encountered [43].

In a systematic review with meta-analysis published in 2020, regarding the correlations between hepatic vascular alterations in patients with COVID-19, the authors found out that this may be due to the endothelial dysfunction (endotheliitis), a procoagulant state, and direct vascular injury of the disease [44].

In a scoping review using a single engine search for studies assessing thrombosis and coagulopathy in COVID-19 patients, studies reported the occurrence of venous thromboembolism and stroke in approximately 20% and 3% of patients, respectively. A higher frequency seems to be present in severely ill patients, in particular those admitted to intensive care units. The thrombotic risk is elevated despite the use of

anticoagulant prophylaxis but optimal doses of anticoagulation are not yet defined. Although an increase of biomarkers such as D-dimer has been consistently reported in severely ill COVID-19, the optimal cut-off level and prognostic value are not known [45].

Recently, Barry et al., have published a portal vein thrombosis in COVID-19 patient [46]. Taking into account that venous thromboembolism is the most thrombotic event reported in patients with COVID-19, venous thrombosis at unusual sites should be considered [47].

In a study from an Italian group of authors, using post-mortem wedge liver biopsies from 48 patients who died from severe pulmonary COVID-19 disease with respiratory failure, collected from two main hospitals in northern Italy, with no clinical symptoms of liver disease or signs of liver failure before and during hospitalization, they showed that there were histological pictures compatible with vascular alterations, characterized by increase in number of portal vein branches associated with lumen massive dilatation, partial or complete luminal thrombosis of portal and sinusoidal vessels, fibrosis of portal tract, focally markedly enlarged and fibrotic [48].

Treatment for PVT includes close monitoring, anticoagulation, thrombolysis, thrombectomy and trans-jugular intrahepatic portosystemic shunt (TIPS). Therefore, the role of a clinician is to understand the range of options and recommend the most appropriate treatment based on these considerations.

Clinical guidelines for PVT management have been published by at least two hepatology societies [49, 50] and several hematology societies [51, 52]. After comparing different guidelines, it is essential to note the following: all guidelines agree with the recommendation of anticoagulation

for acute, non-malignant PVT after careful attenuation of the risk of gastrointestinal bleeding, especially in patients with evidence-associated mesenteric vein extension of small bowel ischemia. Presenting diffuse abdominal pain, as a result, a longer period of time will pass between the onset of the symptoms and the moment of establishing the right diagnosis [53,54,55]. The guidelines differ in terms of duration of anticoagulation: for 3 months, 6 months or indefinitely. In patients with chronic PVT, a strong recommendation for routine anticoagulation could not be made unless an underlying risk factor for neoplasm or thrombophilia could be identified [49, 50].

This COVID-19 pandemic raised some difficulties in global health management, mainly because COVID-19 patients are found to have increased thrombotic risk. In a case report, with a combination of local infection by clostridium difficile and COVID-19 coagulopathy, which led to development of portal vein thrombosis in a patient, published in 2021, its emphasis the fact that, during the current pandemic, clinicians should strongly consider abdominal imaging in patients presenting with abdominal pain due to clostridium difficile infection in the setting of COVID-19 to rule out complications such as portal vein thrombosis. Early diagnosis and treatment of portal vein thrombosis prevent complications of portal hypertension and intestinal infarctions [56].

Conclusions

PVT presents a vague clinical picture, with nonspecific signs and often evolves asymptotically, which makes it difficult to establish an early diagnosis. PVT may occur in acute or chronic conditions in patients with or without cirrhosis. The cornerstone of therapy is anticoagulation, which is mandatory if the patient has intestinal ischemia or a basic pro-coagulant condition.

This presentation summarized the multiple etiological factors leading to PVT. On a background of thrombophilia, and co-infection with *Clostridium difficile* and Sars-Cov2, one should take into consideration this kind of diagnostic, in order not to delay the treatment, and to improve its outcome. We stressed the importance of proper and timely diagnosis of PVT and the recognition of several life-threatening complications, in the hope that more doctors will provide anticoagulation for PVT, which to date remains underreported in general practice.

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